Argus® II Retinal Prosthesis System

HDE #H110002

Ophthalmic Devices Panel Meeting
Food and Drug Administration
September 28, 2012

Agenda

	Presenter
Argus II System Technology	Rob Greenberg, MD, PhD CEO, Second Sight Medical Products
Medical Landscape & Clinical Impact	Julia Haller, MD Ophthalmologist-in-Chief, Wills Eye Institute, Philadelphia, PA
Clinical Trial – Design, Methods & Conduct	Anne-Marie Ripley VP, Regulatory and Clinical Affairs, Second Sight
Clinical Trial - Results	Lyndon da Cruz, MD, PhD Consultant Retinal Surgeon Moorfields Eye Hospital, London, UK
Training and Post-Approval Study	Gislin Dagnelie, PhD Associate Professor of Ophthalmology Johns Hopkins University, Baltimore, MD
Risk-Benefit Assessment & Conclusions	Suber Huang, MD Vice-Chair, Dept. of Ophthalmology & Visual Sciences Case Western Reserve University, Cleveland, OH

Additional Experts

- Eugene de Juan, Jr. MD
  Jean Kelly Stock Distinguished Professor of Ophthalmology
  University of California, San Francisco

- Duane Geruschat, PhD, CLVT, COMS
  Associate Professor, Salus University, Philadelphia, PA
  Research Associate, Johns Hopkins Wilmer Eye Institute, Baltimore, MD

- Mark Humayun, MD, PhD
  Cornelius Ping's Professor of Biomedical Engineering
  Professor of Ophthalmology, Biomedical Engineering, Cell and Neurobiology
  Doheny Eye Institute at University of Southern California, Los Angeles, CA

Who are we trying to help?

- The patients served by the Argus II Retinal Prosthesis System are profoundly blind
  - Bare light perception or no light perception
- They represent a **rare** patient population
  - Retinitis Pigmentosa is a rare disease
  - A small subset of RP patients have declined to bare light perception or worse
    - Approximately 250 new cases/year
- FDA has designated the Argus II System a Humanitarian Use Device
- **There is no cure and no available treatment for this rare population**

Our History

1991	**First use of electrical stimulation of the retina in RP patient**
1998	Company founded
2002	First human implant of an Argus I device at USC (Los Angeles)
2006	First human implant of an Argus II device (in Mexico)
2007	**First Argus II device implanted in a US subject**
2009	Argus II System designated as Humanitarian Use Device by FDA
2011	**Argus II Retinal Prosthesis System CE Mark approval**
2011	**HDE application submitted to FDA**

Second Sight Medical Products, Inc.

- Headquarters and manufacturing in Sylmar, CA
- Facility is ISO 13485 certified and has passed FDA inspection
- Over 100 employees focused on restoring sight to blind individuals
- 13 years and $95 million privately invested in Argus II development
- National Eye Institute, Dept. of Energy, and National Science Foundation provided approximately $105 million to support research and development of Argus retinal prostheses

Humanitarian Device Exemption (HDE)

- Provide incentive for development of devices intended for treatment or diagnosis, **in small patient populations where otherwise a device manufacturer's R&D costs would exceed market returns.**

- HDE criteria:
  - demonstrate reasonable assurance of safety and
  - demonstrate *reasonable basis* to conclude the probable benefit to health outweighs the risk of injury or illness
  - takes into account the probable risks and benefits of currently available devices or alternate forms of treatment (21 CFR 814.118(a)(3)

What does this mean for today's meeting?

- **Safety**: Must be considered in context that these patients have minimal to no residual vision
- **Probable benefit**: Restoration of some vision can have a big impact on these patients' lives
- **Design refinements**: Reasonable and expected in context of studying a rare population for a long period of time
- **Protocol changes**: Reasonable and expected considering that there were few established assessment tools for this population

We will show that the clinical trial of the Argus II System provided scientifically valid evidence that the probable benefits of Argus II System outweighs its risks in this patient population.

The Argus II
Retinal Prosthesis System

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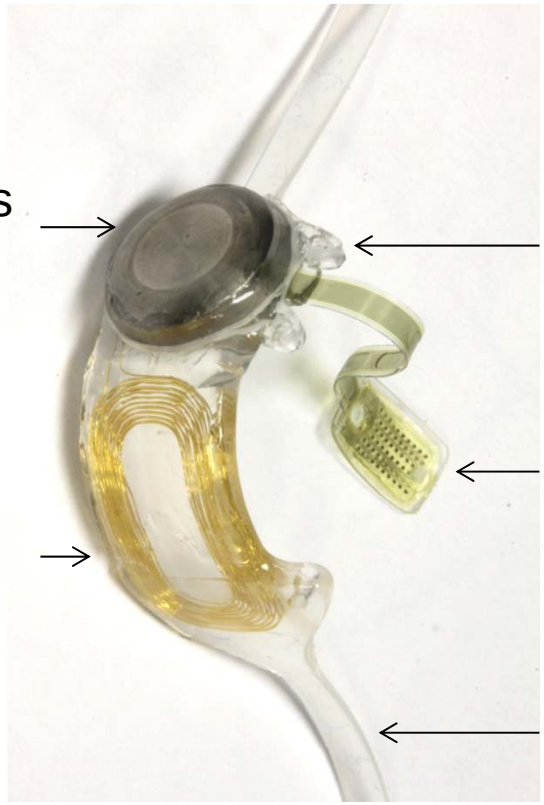
The Argus II Retinal Prosthesis System

External System



Implant

Principle of Operation and Mechanism of Action

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Proposed Indications for Use

The Argus II Retinal Prosthesis System is intended to provide electrical stimulation of the retina to induce visual perception in **blind patients**. It is indicated for use in patients with severe to profound **retinitis pigmentosa** who meet the following criteria:

- Adults, age 25 years or older.
- **Bare light or no light perception in both eyes**. (If the patient has no residual light perception, then evidence of intact inner layer retina function must be confirmed.)
- Previous history of useful form vision.
- Aphakic or pseudophakic. (If the patient is phakic prior to implant, the natural lens will be removed during the implant procedure.)
- Patients who are willing and able to receive the recommended post-implant clinical follow-up, device fitting, and visual rehabilitation.

The Argus II implant is intended to be implanted in a single eye, typically the worse-seeing eye.

Evolution of the Argus II Implant

"Single Metal" Version
n=15 subjects
Implanted 2007-2008

3/15 Single Metal implants had a small "slot" in the transcleral region of cable to improve manufacturing yields.

"Dual Metal" Version
n=15 subjects
Implanted in 2009

Main Changes:

- Reduced cable width and increased its flexibility
- Molded silicone on the array and cable
- Made tack shorter and tack spring stiffer
- Reduced the height of the electronics case
- Reinforced suture tabs and added a tab to the electronics case

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Impact of Device Modifications During the Trial

- Design modifications must be considered in context of clinical study of pioneering technology that took a long time to enroll, with long-term follow-up
- Modifications were:
  - Incremental
  - Thoroughly tested and verified on the bench
  - Reviewed and approved by the FDA prior to implementation in the clinical trial

- **Sub-group analysis of Single-Metal vs. Dual-Metal cohorts showed no significant differences in performance and modest improvements in safety for the Dual-Metal cohort**
- **Modifications did not alter the principle of operation, mechanism of action, or indications for use**

Planned Changes to Marketed Version of the Systems

"Dual Metal" Version

Planned Commercial Version

Planned Changes:

- Edge of coil suture tab rounded slightly
- Changed the radio frequency at which the glasses communicate to meet new international radio communication standards
- Modified the implant chip to improve wireless link between the glasses and the implant
- Externals modified primarily to improve ergonomics and ease of programming

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Planned Changes to Marketed Version of Implant

- "FDA's review of the preclinical testing for these modifications does not raise significant safety concerns…" *
- Stimulation output for the commercial implant is identical to that of the clinical trial implant.

➢ **Commercial design has been thoroughly tested and verified on the bench. Changes do not require testing in a clinical trial.**

* From FDA Executive Summary (p. 14)

Implant Long-Term Reliability

- Implant designed to be permanent
- Extensive bench testing supports device functionality to at least 5 years
- Clinical data supports the bench test results:
  - 30 Devices implanted for a cumulative total of >105 subject-years
  - 8 subjects implanted ≥ 5 years as of today
  - 1 implant failure at 4 years attributable to damage at time of surgery

➢ **Argus II Implant is reliable for long-term implant**

Implant Long-Term Reliability

- Average number of electrodes enabled prior to implant: 55.5
  - Analysis provided to FDA showed that the number of electrodes enabled prior to implant did not correlate with performance
- All subjects used the system at home as of last follow-up, despite a variable number of enabled electrodes

Summary

- Novel, pioneering technology
- Device reliable for long-term implant
- Sustained development effort that has spanned over two decades
- $200 million in public and private money has been invested
- Technology is intended to help a rare population with no currently available therapies

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The Medical Landscape and Clinical Impact of the Argus II System

Julia A. Haller, MD

Ophthalmologist-in-Chief,
Wills Eye Institute, Philadelphia, PA

Professor and Chair, Dept. of Ophthalmology
Jefferson Medical College, Thomas Jefferson University

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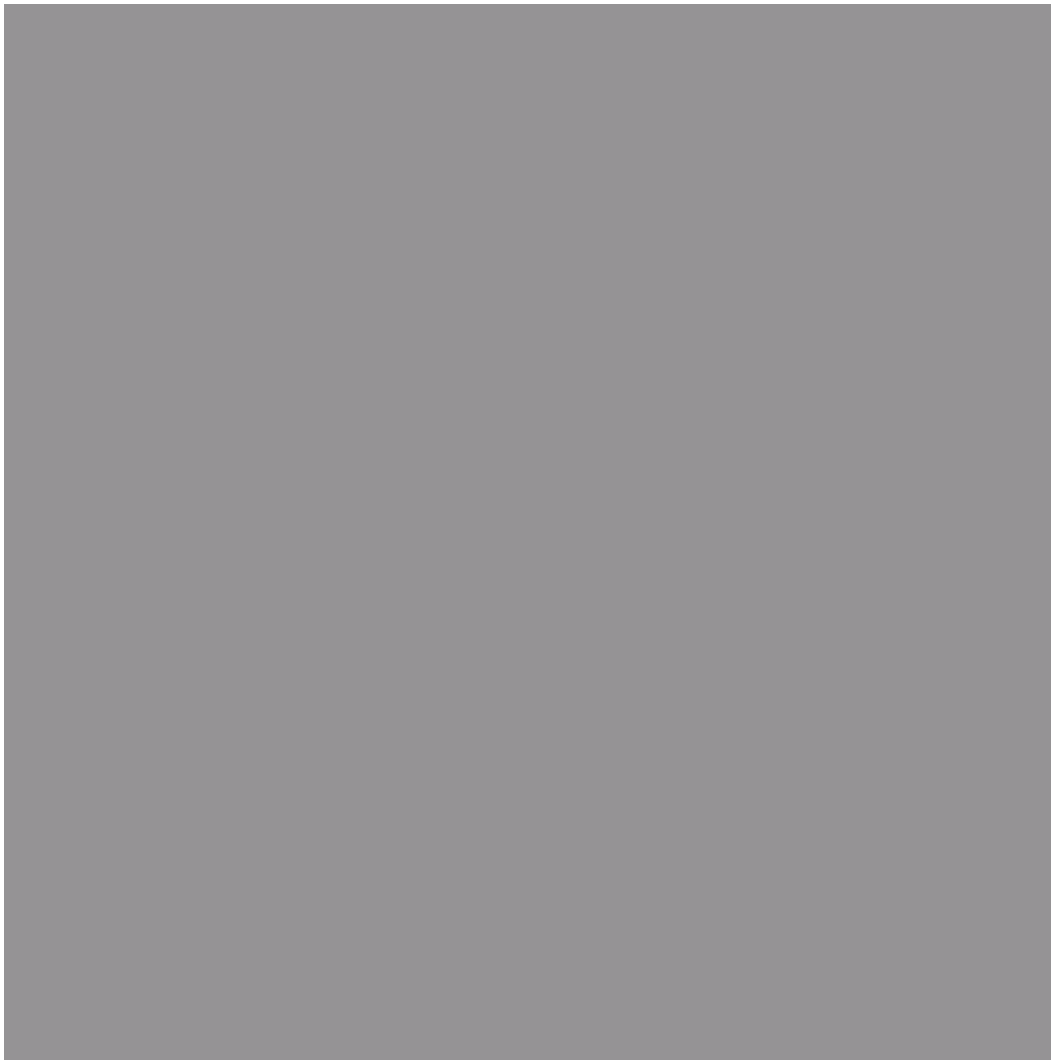
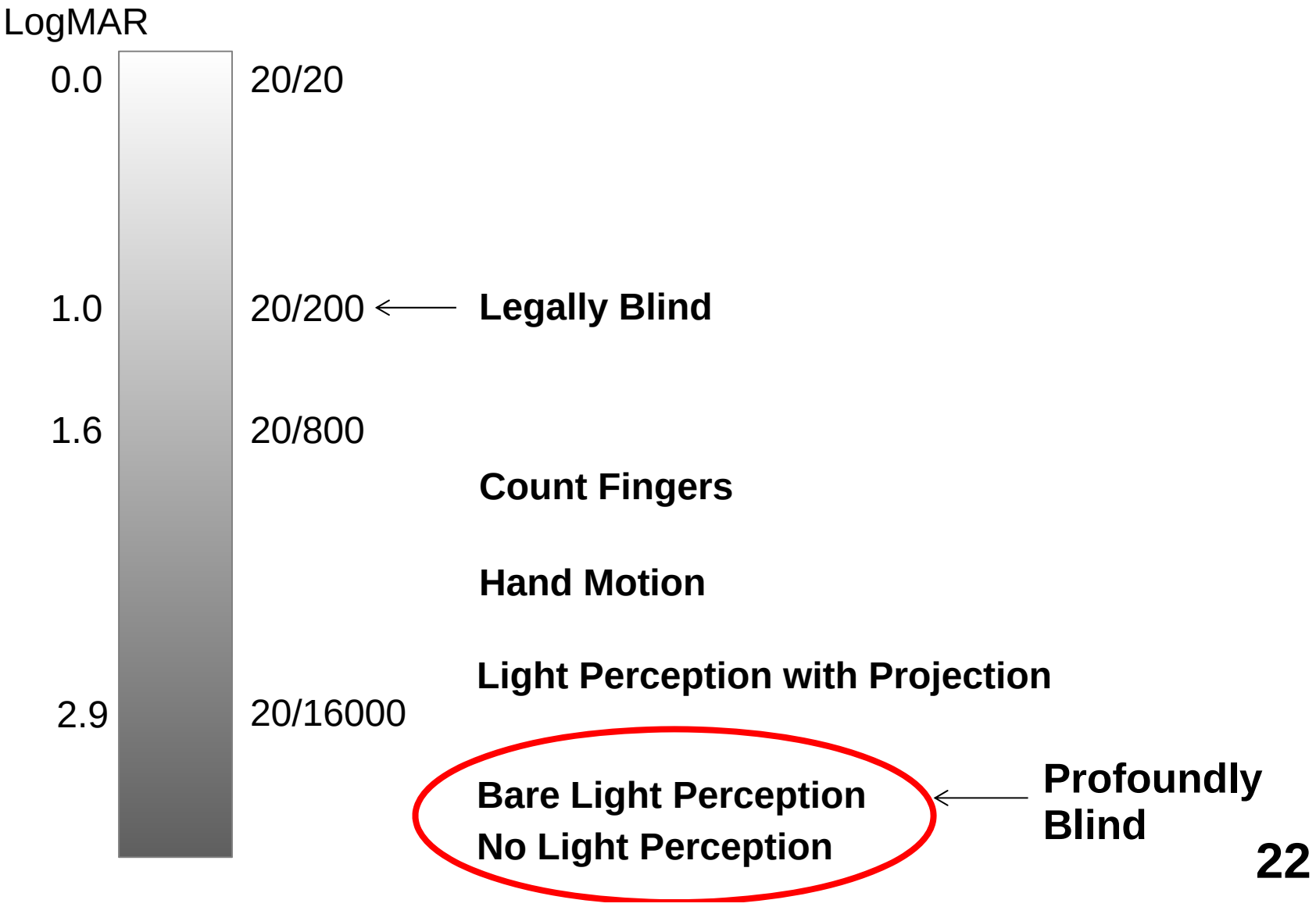
Progression of blindness in RP



What does “blind” mean?



Impact of Blindness

- This patient population is profoundly blind, with little or no functional vision
- Loss of visual field is associated with:
  - Decrease in physical mobility
  - Increase in the number of accidents and injuries
- Blindness later in life is associated with depression and anxiety
- Research by Brown et al.
  - Time trade-off utility associated with no light perception is 0.26, which is the same as severe stroke with aphasia
  - The only non-terminal condition that ranks worse is severe stroke with total paralysis

Brown et al. *Can J Ophthalmol* 2005 40: 277-287.

No Currently Available Therapies

- **There are no therapies currently available for the small subset of RP patients with profound visual loss**
- Experimental research options
  - Most target earlier stages of the disease
  - Most designed to slow progression, but don't reverse vision loss
  - Years away from market approval in the U.S.
- Patients, families, and physicians are eager for options

Clinical Impact of the Argus II System

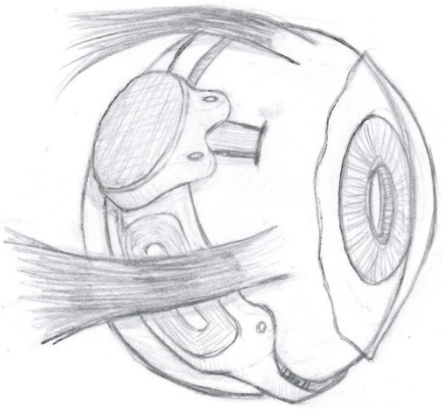
- Argus II system can improve patient's orientation and mobility, activities of daily living, and well-being:
  - Locate doors and windows
  - Sort light and dark clothes
  - Stay within a crosswalk
  - Avoid obstacles
  - Feel more socially connected
  - Enjoy being "visual" again
  - Tracking players on a field
  - Watching fireworks

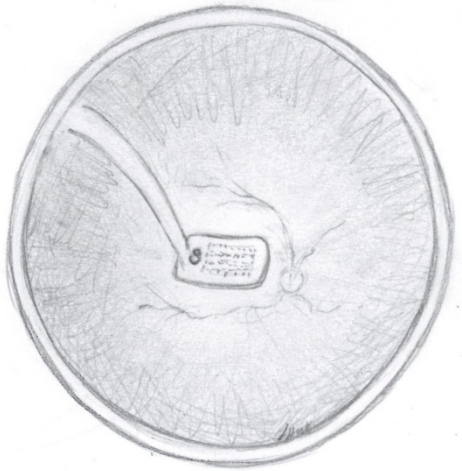
Implantation and Follow-Up Procedures

Argus II Surgical Procedure

Implant procedure requires a combination of skills well known to vitreoretinal surgeons:

- Lens removal, if applicable
- Peritomy & muscle isolation
- Device placement
- Anchor suture tabs
- Secure scleral band
- Vitrectomy
- Create sclerotomy
- Insert array
- Close sclerotomy
- Tack so array is over macula
- Apply graft
- Close
- Post-op medication





Post-Implantation Follow-Up

- Routine clinical follow-up
- Custom-programming the Video Processing Unit
- In-clinic training

Summary

- Argus II System is intended for patients who are **profoundly blind** due to Retinitis Pigmentosa
  - RP is a rare disease that qualifies our device as a Humanitarian Use Device
  - Blindness has a devastating impact on patients and their families
  - Patients are in extreme need of a treatment
  - Risk assessment
    - Adverse events have very different implications for someone who is profoundly blind vs. normally sighted or even legally blind
- Device is implanted using standard surgical techniques that vitreoretinal surgeons routinely perform

Argus II Clinical Trial: Design, Methods and Conduct

Anne-Marie Ripley

VP, Clinical & Regulatory Affairs

Second Sight Medical Products, Inc.

Study Design

- **Objective**
  - Evaluate safety and probable benefit of the Argus II System
- **Design**
  - Prospective, single-arm, multi-center, feasibility study
  - Subjects served as their own control: System ON vs. OFF
- **Sample Size**
  - 30 subjects
- **# Centers**
  - 10 centers: 6 in US, 4 in Europe

Study Design (cont.)

- **Follow-Up Duration**
  - Initially, 3 years minimum per subject
  - Study follow-up extended to 7 years
    - Allow subjects to continue to use the device while we were going through regulatory review process with the FDA
    - Collect additional long-term follow-up data
- **Data Analysis**
  - Not a hypothesis driven study
  - Not powered for statistical analyses of endpoints
  - Confidence intervals large due to small sample size

Key Subject Inclusion Criteria

- Retinitis pigmentosa with bare light or no light perception in both eyes
- Perception of light, either natural or electrically induced, in implanted eye
- History of useful form vision
- ≥ 50 years old
  - Criterion changed to ≥ 25 years old beginning in 2009 to facilitate enrollment
- Willing and able to comply with the study requirements

Key Subject Exclusion Criteria

- Optic nerve disease
- Diseases or conditions that:
  - Affect retinal function
  - Obscure view of retina or the anterior segment
  - Impede implantation or function of the device
  - Prevent appropriate consenting
- Unrealistic expectations of the System
- Axial length <21.5 or >26.0 mm in the implanted eye (Criterion added in 2008 at request of FDA.)

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Challenges in Designing a Study for a Rare Population

- Rare disease such as RP
  - Large, randomized controlled trial not possible
  - Difficult to recruit subjects
- Lack of commonly accepted assessment tools:
  - In 2006, organized a meeting of experts in low vision assessment tools and techniques to advise on assessment
  - Adjustments were made to the assessments as study progressed

Study Endpoints

Primary Endpoints:

- Safety: Adverse event rates
- Probable Benefit: Visual Function (e.g. visual acuity)

Secondary Probable Benefit Endpoints:

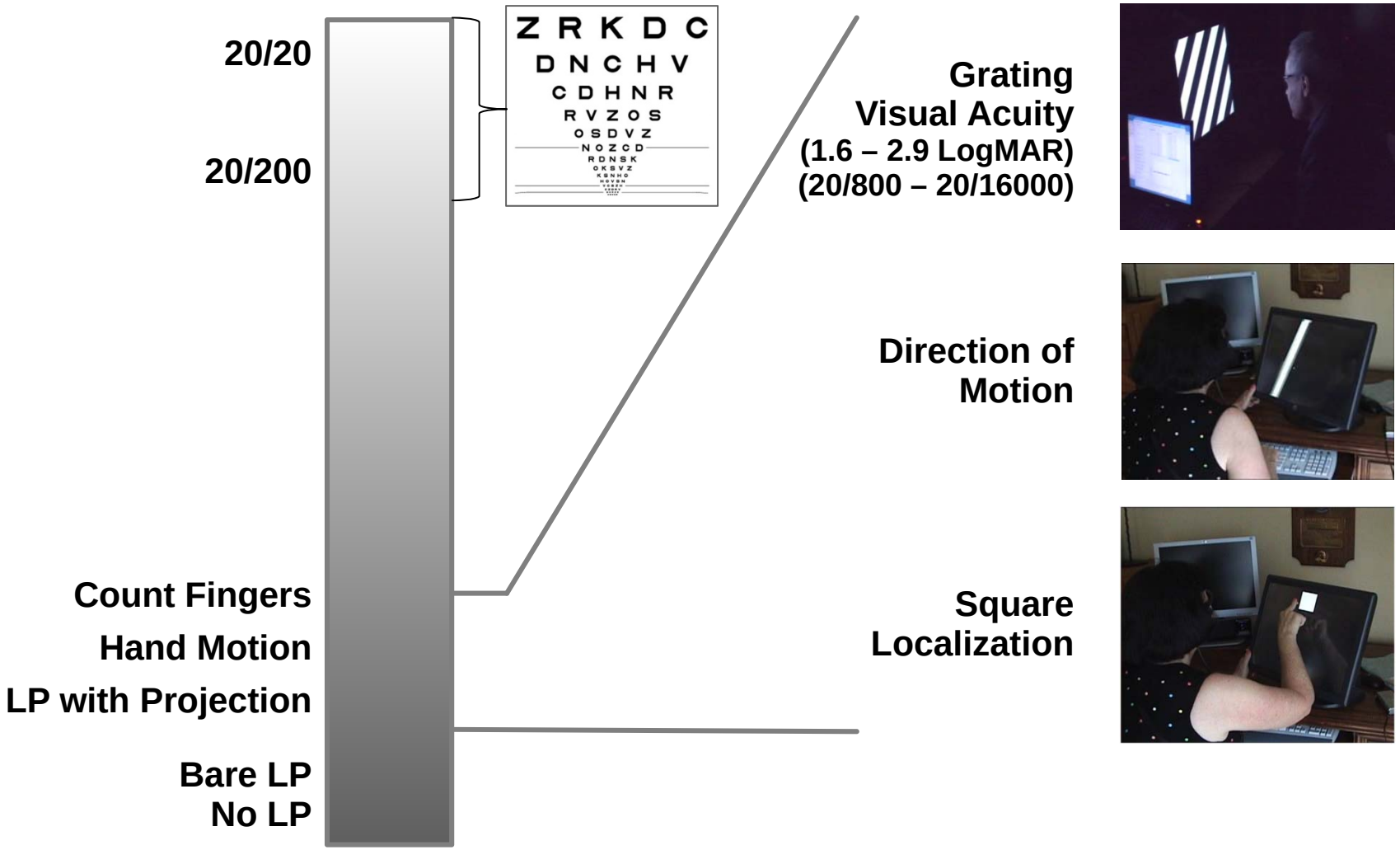
- Functional Vision (how vision is used in everyday life)
- Quality of Life

Primary Safety Endpoint

- Investigators reported all adverse events per protocol definitions and classified each event as:
  - Serious or Non-serious
  - Surgery-, device- or subject-related

- Independent Medical Safety Monitor (IMSM)
  - Suber Huang, MD (Case Western Reserve, Cleveland, OH)
  - Reviewed and adjudicated all reports
    - Ensured consistency in reportable terms and classifications
    - IMSM never changed the investigator's classification of an event from serious to non-serious

Visual Function Assessments



LP = Light Perception

Visual Function Assessments – Additional Research

Character Recognition

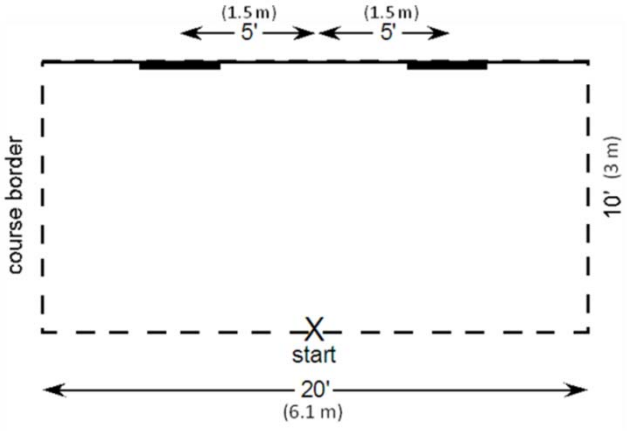
Reading Words

Secondary Study Endpoints

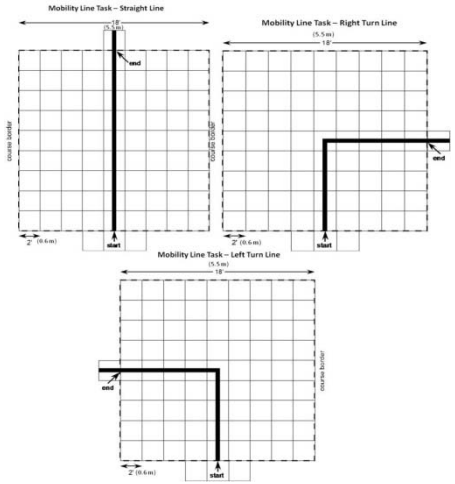
- **Functional Vision and Quality of Life (QOL)**
  - Orientation and Mobility Tests
  - 3 Functional Vision Tasks (additional research)
  - Functional Low-Vision Observer Rated Assessment (FLORA)
  - 2 questionnaires:
    - Massof Activity Inventory
    - Visual Quality of Life (VisQOL)

Orientation and Mobility Tests

Door Test



Line Test



Functional Vision Tasks – Additional Research

Sock Sorting

Sidewalk Tracking

Direction of Walking

Functional Low-Vision Observer Rated Assessment (FLORA)

- In 2010, FDA requested that we conduct a real-world assessment of our subjects
  - Developed FLORA in consultation with the FDA
  - Added it to the study in 2010
- Observer-rated assessment used to evaluate:
  - How do subjects use the Argus II System in their lives?
  - What effect does the Argus II System have on their quality of life?
- Performed by trained, certified low-vision therapists who used standard low-vision assessment techniques
- 4-6 hours was committed to completing the FLORA with each subject

Study Conduct

- Non-randomization of testing
  - Device ON testing performed first majority of time
  - Doing the ON test first familiarizes subject with the test and could improve performance with System OFF
- Evaluators were unmasked
  - Not possible to mask the evaluators because subjects behaved very differently when using the System vs. when not using the System
  - All visual function tests were computer driven, and most did not require any evaluator input

Study Conduct (cont.)

- Protocol Deviations
  - Vast majority had no impact on outcome of the study
  - Worst case analysis performed to assess impact of missing data showed no substantial effect on results
  - Did not affect the scientific validity of the study
- Protocol Modifications
  - FDA suggested several protocol changes, and reviewed and approved all protocol changes
  - 3 newly developed assessments added during the course of the study
    - Changes added to amount of data to support probable benefit
  - Orientation and Mobility courses were modified

Study Design and Methods Conclusions

- Challenges in designing and conducting this trial
  - First-of-its-kind technology for a rare patient population
  - No precedent for designing a trial where the goal is to partially restore vision to blind patients
- Addressed these challenges by:
  - Choosing the best available assessments at the time the study was designed
  - Modifying and adding assessments to better characterize the benefit provided to subjects by the device
  - Performing the assessments at pre-defined time points, using the same methods on all subjects
  - Obtaining long-term follow-up data on all subjects

The study design and conduct were reasonable and appropriate for an HDE

Argus II Clinical Trial - Results

Dr. Lyndon da Cruz, PhD, MBBS, FRCOphth

Consultant Retinal Surgeon

National Institute of Health Research,
Biomedical Res. Centre for Ophthalmology

Moorfields Eye Hospital and University College, London

Clinical Trial Sites

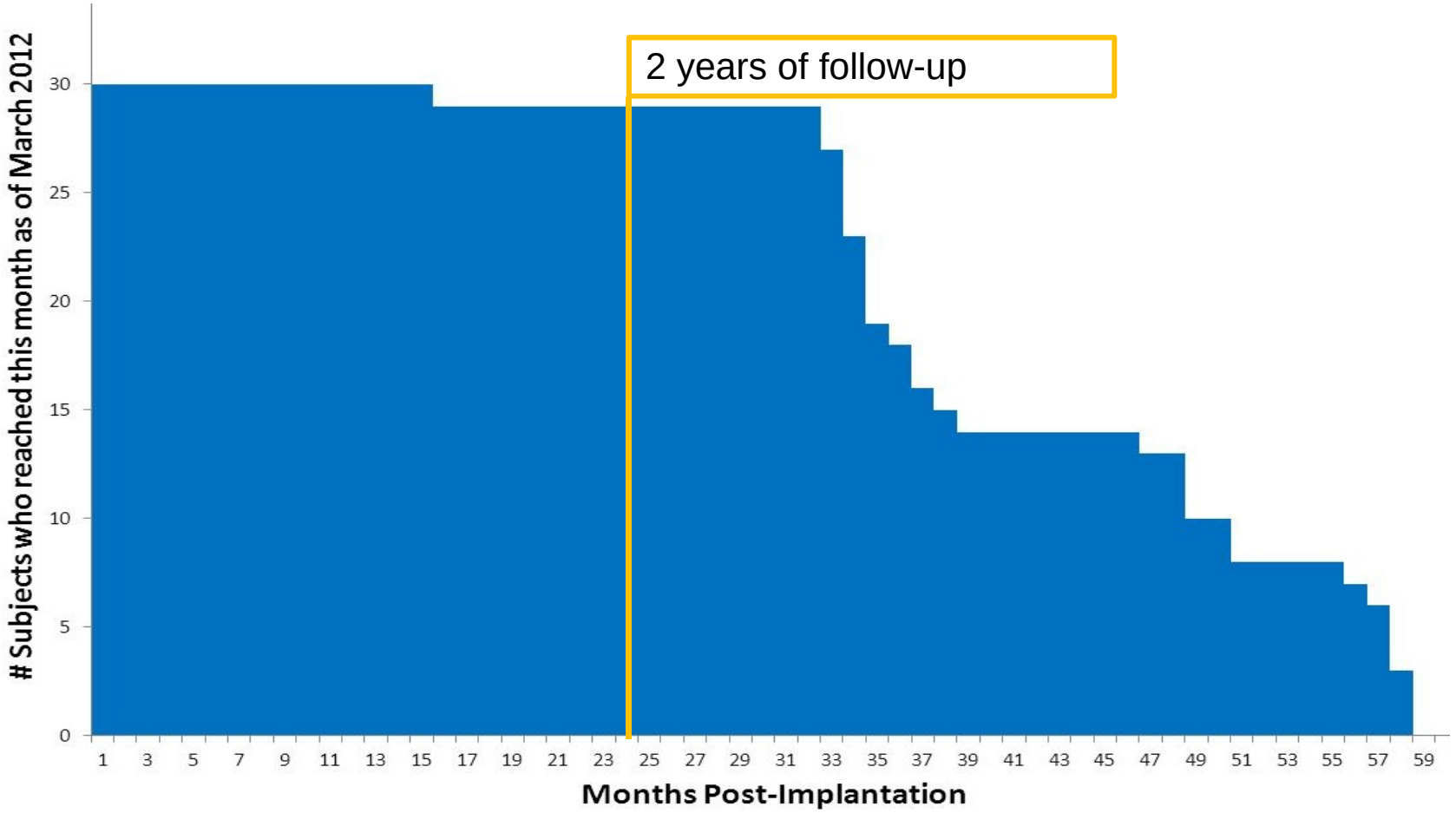
Site	# Subjects
Moorfields Eye Hospital (London, UK)	7
Johns Hopkins Hospital (Baltimore, MD)	5
Le Centre Hospitalier National D'Ophthalmologie de Quinze-Vingts (Paris, France)	4
Manchester Royal Eye Hospital (Manchester, UK)	3
University of Southern California (Los Angeles, CA)	2
University of California San Francisco (San Francisco, CA)	2
Retina Foundation of the Southwest (Dallas, TX)	2
Scheie Eye Institute and Wills Eye Hospital (Philadelphia, PA)	2
Hôpitaux Universitaires de Genève (Geneva, Switzerland)	2
Columbia University and Lighthouse International (New York, NY)	1

Enrollment and Duration of Follow-up

Enrollment	June 2007 – August 2009
Data cut-off date	March 15, 2012
Mean ± SD follow-up	3.5 ± 0.9 years
Range follow-up*	2.6 – 4.8 years
Total cumulative subject-years	105
Device Failure	1 (4 years post-implant)
Device Explant	1 (1.2 years post-implant)

* Minimum implant duration excludes the one explanted subject

Amount of Follow-Up Data



Baseline Characteristics

	Average	Range
Age at time of implant (years)	58	28 – 77
	#	**Percent**
Gender		
Female	9	30%
Male	21	70%
Diagnosis		
Retinitis Pigmentosa*	29	97%
Choroideremia	1	3%
Residual Vision at Baseline, implanted eye		
Bare Light Perception	29	97%
No Light Perception	1	3%

* 1 had Leber Congenital Amaurosis

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Implantation Surgery Results

- Average implantation surgery: 4 hours
- All 30 subjects successfully implanted
  - 13 surgeons
  - 10 centers worldwide

Study Endpoints

Primary Endpoints:

- Safety: Adverse event rates
- Probable Benefit: Visual Function (e.g. visual acuity)

Secondary Probable Benefit Endpoints:

- Functional Vision (how vision is used in everyday life)
- Quality of Life

Primary Study Endpoints

- **Safety**
- Probable Benefit - Visual Function
  - Square localization
  - Direction of motion
  - Grating visual acuity
  - Character recognition and reading words (Additional research)

Safety Overview

- No loss of an eye due to AEs
- Despite AEs, Argus II System continued to work in all subjects
- AEs were resolved using standard treatment methods
- AEs did not result in a loss of residual native vision
- Safety must be considered in the context of the profoundly blind subjects

Definition of a Serious Adverse Event

- SAEs were defined per FDA regulations (based on 21 CFR 803.3)
- Protocol defined serious adverse events as medical occurrences that:
  - Caused death
  - Were life threatening
  - Caused permanent impairment of a body function or permanent damage to body structure
  - Necessitated medical or surgical intervention to preclude permanent impairment, or
  - Required hospitalization

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Serious Adverse Events (SAE)

Device- or Surgery-Related Events

	# of Subjects (n=30)	# of Events	% of subjects
Hypotony	4	4	13.3%
Conjunctival erosion	3	4	10.0%
Intraocular inflammatory events:			
Presumed endophthalmitis - culture negative	3	3	10.0%
Uveitis	1	1	3.3%
Conjunctival dehiscence	3	3	10.0%
Fibrotic events:			
Retinal detachment – rhegmatogenous	1	1	3.3%
Retinal detachment - tractional and serous	1	1	3.3%
Retinal tear	1	1	3.3%
Re-tack	2	2	6.7%
Corneal melt – infective	1	1	3.3%
Corneal opacity	1	1	3.3%
Keratitis – infective	1	1	3.3%

SAE - Conjunctival Erosion / Dehiscence

- 5 subjects:
  - 2 subjects with dehiscence 1-2 months post-implant
    - Resolved with no recurrence
  - 1 subject with erosion then dehiscence 1.5 months post-implant
    - Resolved with no recurrence
  - 2 subjects with erosion 9-12 months post-implant
    - 1 subject ultimately explanted due to recurrent erosion.
    - 1 subject has had recurrent erosion, but is currently stable and still implanted.
- No cases of endophthalmitis associated with conjunctival erosion or dehiscence

SAE - Presumed Endophthalmitis

- 3 subjects:
  - All three culture-negative
  - 1 in the immediate post-operative period
  - 2 within 5-8 weeks post-implant

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SAE - Presumed Endophthalmitis

- No cases associated with pre-existing conjunctival erosion or hypotony
- All cases resolved completely with medical management
- None required explantation
- Adjustments made to surgical technique and operating room management to address these events
- After these adjustments implemented there were no further cases of presumed endophthalmitis in next 15 subjects

SAE - Retinal Detachment

- 2 cases
  - 1 precipitated by a blow to the eye which the investigator felt was contributory to the detachment
  - 1 caused by traction on the retina attributed to insufficient removal of vitreous at the time of implant surgery
- Retina under array attached in both subjects
- Both subjects still able to use the device

- Surgeon Manual emphasizes the need to completely remove the posterior vitreous
- Second Sight surgeon training* emphasizes how to monitor for and treat a RD

* FDA has not formally reviewed this training program

SAE - Hypotony

- Hypotony defined as IOP ≤ 5mmHg
- 4 subjects
  - Onset
    - 2 occurred between 2-5 months
    - 1 occurred at 1 year
    - 1 occurred at 2 years
  - Comorbidity
    - 3 occurred in conjunction with eye insults (repeated conjunctival erosion with surgical interventions, uveitis/endophthalmitis, uveitis/vitreous band traction)
    - 1 occurred in a subject with chronic, bilateral low IOP

SAE - Hypotony

- Hypotony is a risk associated with any device where a portion of the device is placed permanently through the eye wall.

- Minor changes made to the implant cable to address hypotony which led to a reduction in the number of hypotony events (serious and non-serious)

Serious Adverse Events

	No or non-serious AEs only	SAE(s) that resolved with treatment or minor interventions	SAEs that required multiple or significant interventions
# Subjects	19	7	4
# SAEs	0	10	13

- **19 subjects with no SAEs**
- **4 subjects with SAEs that required multiple or significant interventions**

4 Subjects with "Significant" SAEs

Subject ID	Intraocular Procedures	Interventions	Current Status
6	1	Repair of RD	Resolved
13	1 (explant)	Explant	Resolved
16	3	Re-tack, gas, and silicone oil (for hypotony)	Resolved
30	4	Re-tack, repair of RD x3	Stable

- 4 subjects experienced 13 SAEs and 34 non-serious AEs
  - No phthisical eye
  - No loss of residual vision
  - No loss of eye
  - 1 subject has ongoing mild-moderate, intermittent pain (suture irritation)

Serious vs. Non-Serious AEs

- Examples of AEs that could be SAEs or non-serious AEs:
  - Hypotony
  - Uveitis
  - Fibrotic events (e.g. epiretinal membrane)
- Non-Serious Events:
  - Did not cause permanent impairment of a body function or permanent damage to body structure,
  - Did not necessitate medical or surgical intervention to preclude permanent impairment, or
  - Did not require hospitalization or prolonged hospitalization.

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Non-Serious Adverse Events

Device- or Surgery-Related Events

	# of Subjects	# of Events	% Subjects (n=30)
Pain – ocular	9	17	30.0%
Fibrotic events:			
Proliferative vitreoretinopathy (PVR)	1	1	3.3%
Retinal detachment – tractional	1	1	3.3%
360° Circumferential vitreous band traction	1	1	3.3%
Epiretinal membrane	11	11	36.7%
Fibrosis around the tack	1	1	3.3%
Intraocular Inflammatory events:			
Uveitis	5	6	16.7%
Inflammation – ocular	4	4	13.3%
Ocular fibrin	1	1	3.3%
Keratic Precipitates	2	3	6.7%
Conjunctival congestion	10	11	33.3%
Elective revision surgery	7	7	23.3%
Hypotony	7	7	23.3%
Suture irritation	6	7	20.0%
Choroidal detachment	6	6	20.0%
Conjunctivitis – inflammatory	4	5	13.3%
Retinal thickening - cystoid macular edema (CME)	5	5	16.7%
Retinal thickening - without cystic changes	4	4	13.3%
Vitreous hemorrhage	4	4	13.3%
Headache	3	3	10.0%
High IOP	2	3	6.7%
Hyphema	3	3	10.0%
Corneal vascularization	2	2	6.7%
Epiphora	2	2	6.7%

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Non-Serious Adverse Events (cont.)

	# of Subjects	# of Events	% Subjects (n=30)
Choroidal effusion	1	1	3.3%
Conjunctival cyst	1	1	3.3%
Conjunctival dehiscence*	1	1	3.3%
Conjunctival erosion*	1	1	3.3%
Corneal abrasion	1	1	3.3%
Corneal dryness	1	1	3.3%
Corneal epithelial defect	1	1	3.3%
Corneal filaments	1	1	3.3%
Corneal fold	1	1	3.3%
Corneal suture broken	1	1	3.3%
Decrease in light perception	1	1	3.3%
Filamentary keratitis	1	1	3.3%
Nausea	1	1	3.3%
Nystagmus increase	1	1	3.3%
Ptosis	1	1	3.3%
Retinal detachment - serous	1	1	3.3%
Retinal folds	1	1	3.3%
Retinoschisis	1	1	3.3%
Rubeosis	1	1	3.3%
Scleral patch displacement	1	1	3.3%
Scleritis	1	1	3.3%
Subconjunctival eyelashes	1	1	3.3%
Vertigo	1	1	3.3%

Stability of the Implant

Array Rotation	# Subjects
No rotation of the array	19
Array rotated approximately 0.1 – 0.2 mm	3
Array rotated approximately 0.3 - 0.4 mm	7
Array rotated approximately 0.8 mm	1

- Rotations occurred in the first 3-6 months in 10/11 subjects
- Rotations did not lead to any AEs
- No revision surgery was performed to treat array rotation
- Rotation did not lead to any notable change in performance

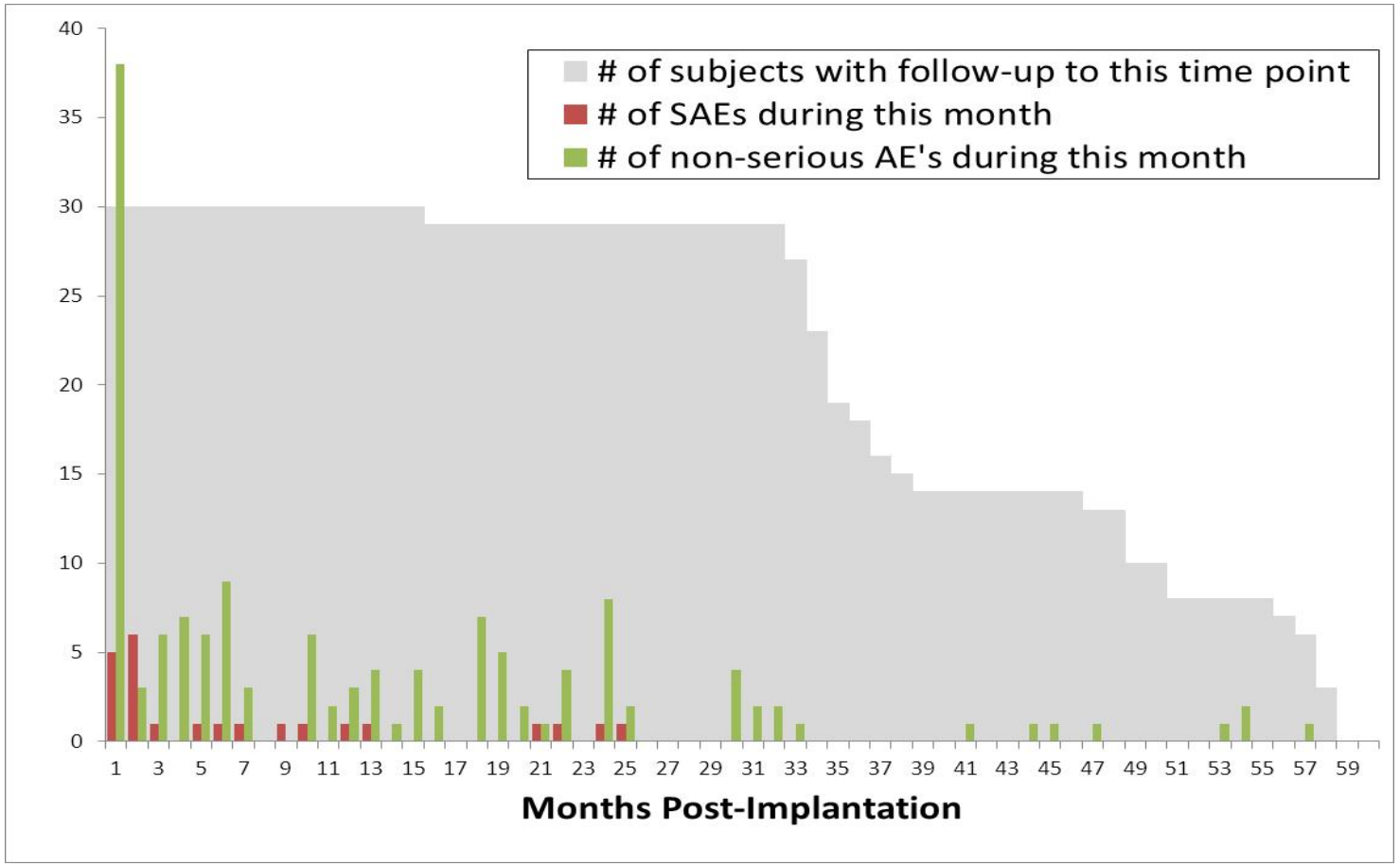
Surgical Re-Interventions

- 9 subjects required surgical re-interventions to treat an SAE
    - All SAEs, with exception of endophthalmitis and uveitis, required a surgical intervention(s) to treat
    - Standard techniques were used for these procedures
- 7 subjects had elective revisions surgeries (i.e. augmentation)
    - Procedures performed to improve performance
    - All were considered non-serious AEs.

Safety Summary

Adverse Event Rates and Onset

Most events occurred in the first 6 months post-implant.
After 2 years post-implant, there have been no new serious adverse events and very few non-serious events.



Safety Conclusions

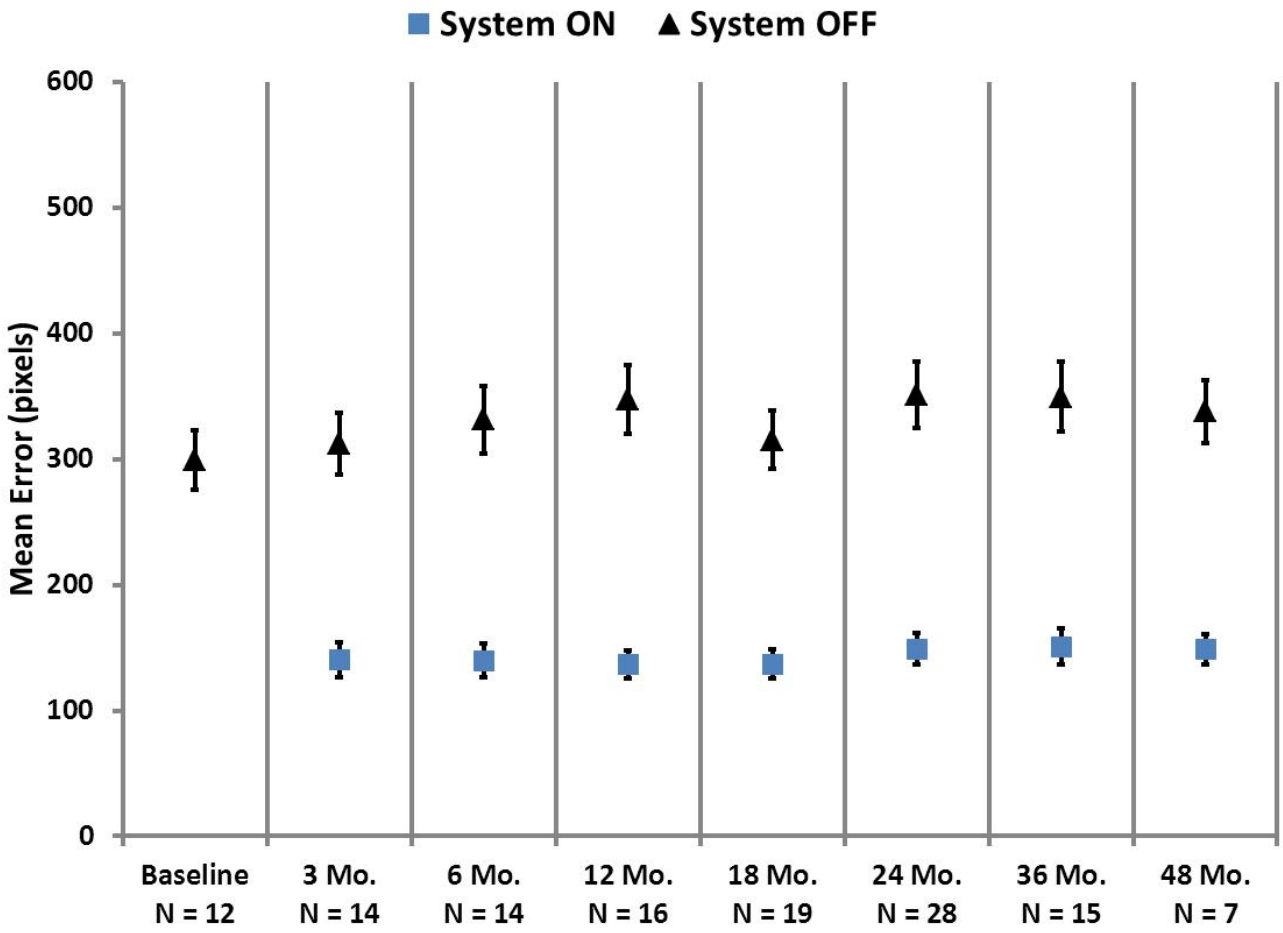
- Despite AEs, Argus II System continued to work in all subjects (except the one who was explanted)
- Rates of AEs were acceptable; confidence intervals wide due to small number of subjects
- Most AEs were resolved using standard treatment methods
- One subject required explant
- One subject has SAEs that are stable but unresolved
- No loss of an eye due to AEs
- AEs did not result in a loss of residual native vision
  - Only loss of residual native vision in the implanted eye (i.e. BLP to NLP) occurred bilaterally

➢ **Reasonable assurance of safety demonstrated when considering the probable benefit**

Primary Study Endpoints

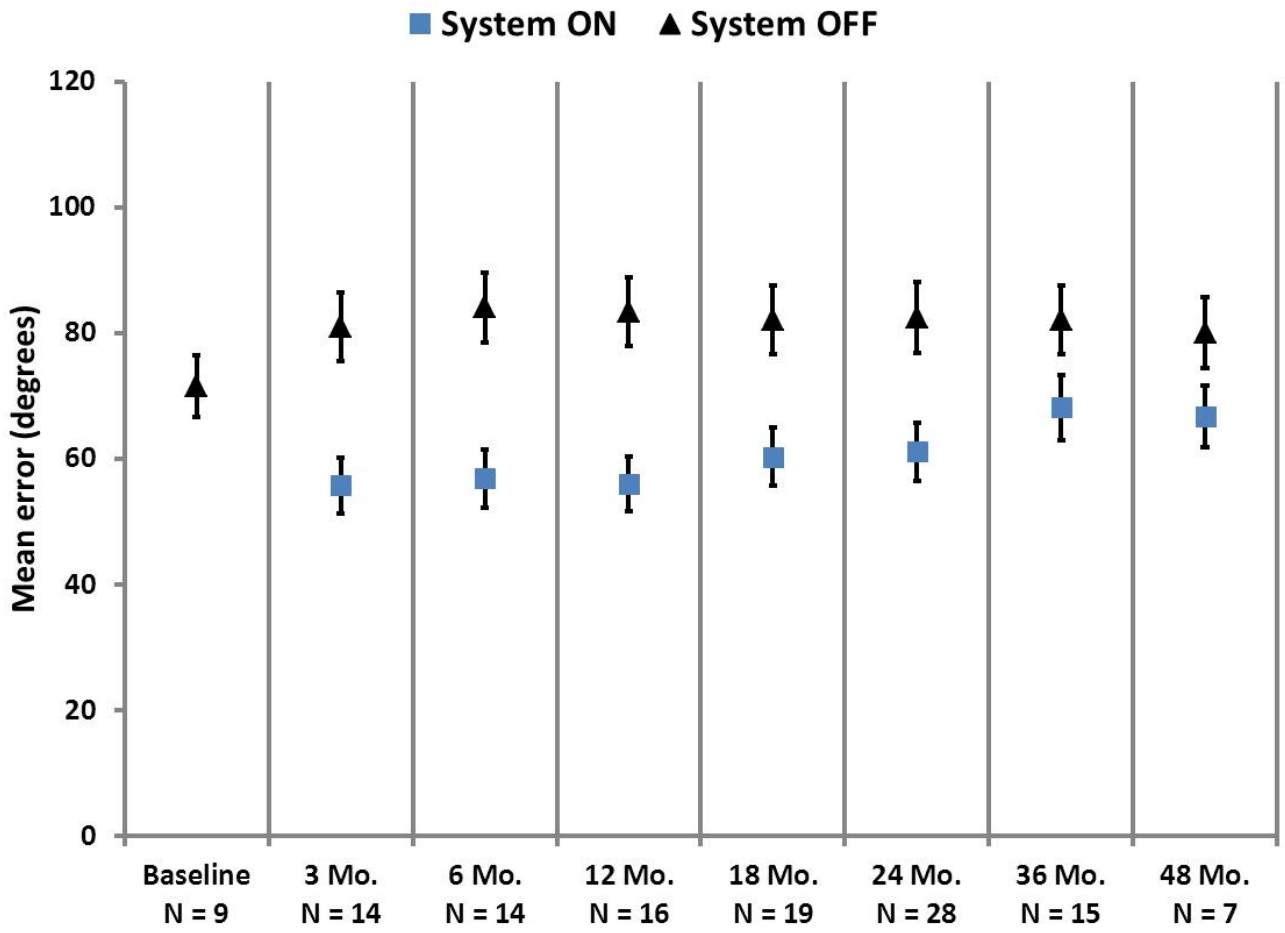
- Safety
- **Probable Benefit - Visual Function**
  - Square localization
  - Direction of motion
  - Grating visual acuity
  - Character recognition and reading words (Additional research)

Visual Function - Square Localization



- **The Argus II System improved subjects' ability to locate an object**

Visual Function - Direction of Motion



- **The Argus II System improved subjects' performance on a spatial vision task**

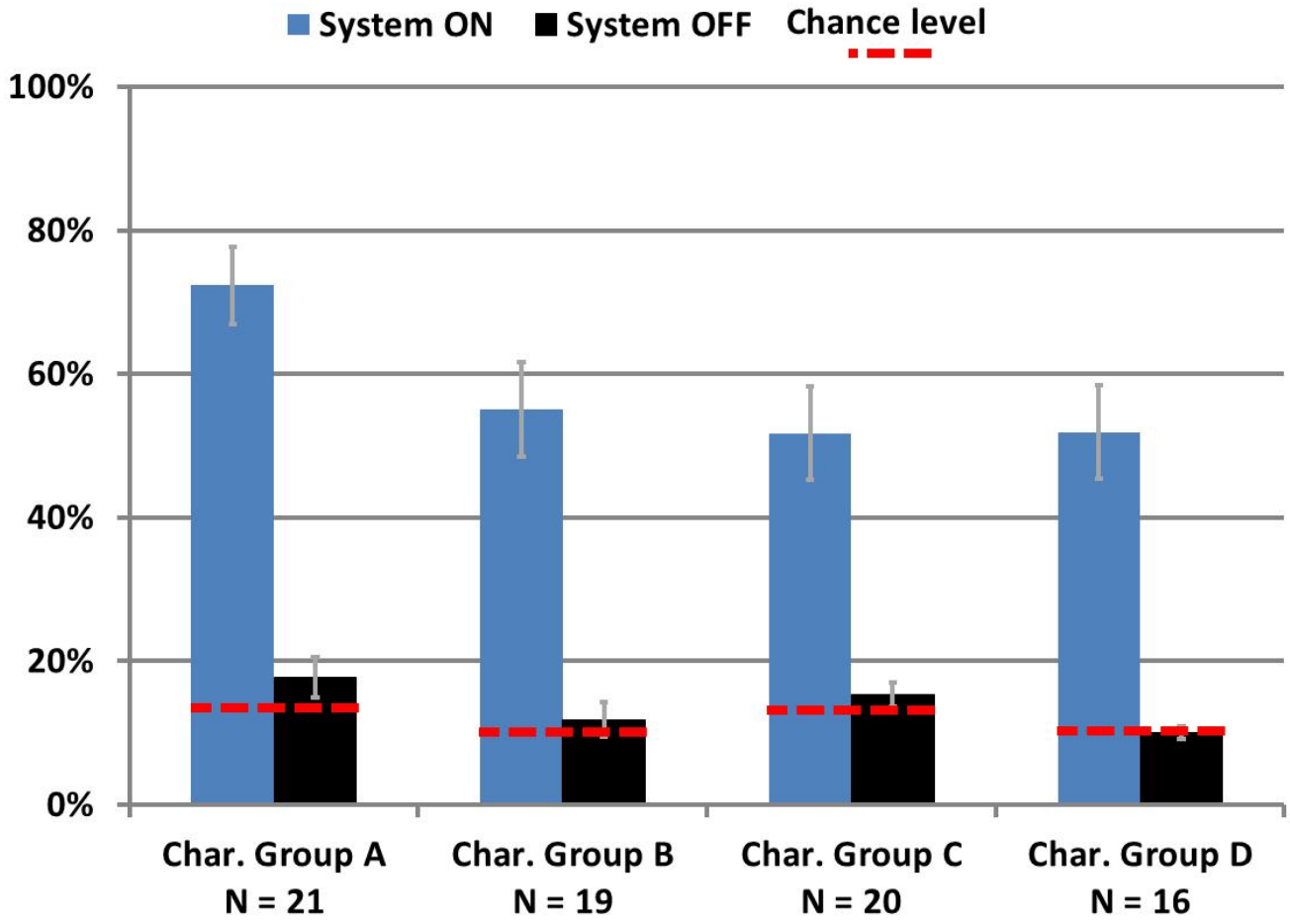
Visual Function - Grating Visual Acuity

	% of Subjects Whose Visual Acuity Improved to Better than 2.9 LogMAR (n=30 subjects)
System ON	27% (n=8)
System OFF, Implanted Eye	0% (n=0)
System OFF, Fellow Eye	0% (n=0)

Best score was 1.8 logMAR (20/1262)

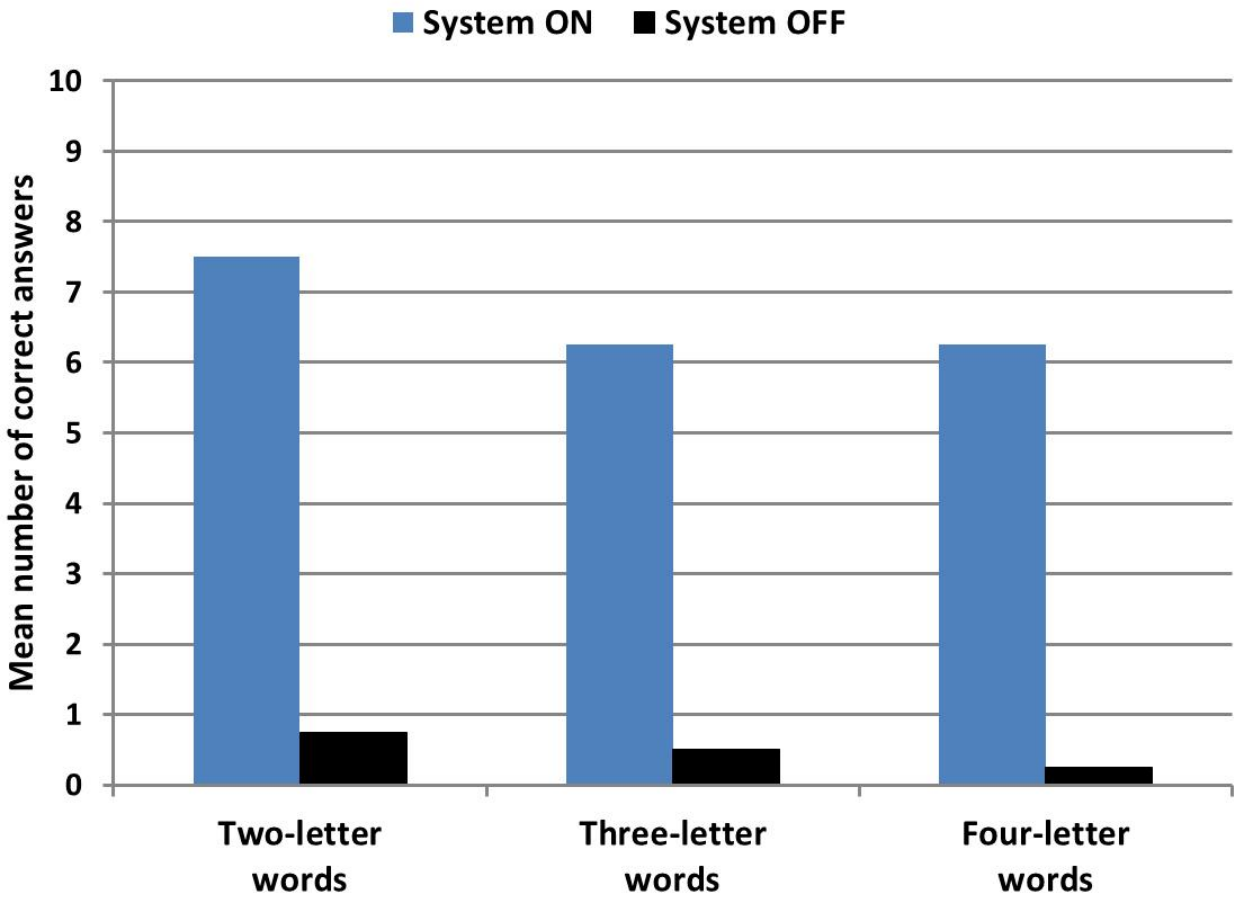
- **About ¼ of subjects regained a measurable visual acuity**

Visual Function - Character Recognition



- On average, Argus II System improved subjects' ability to identify large letters

Visual Function – Reading Words

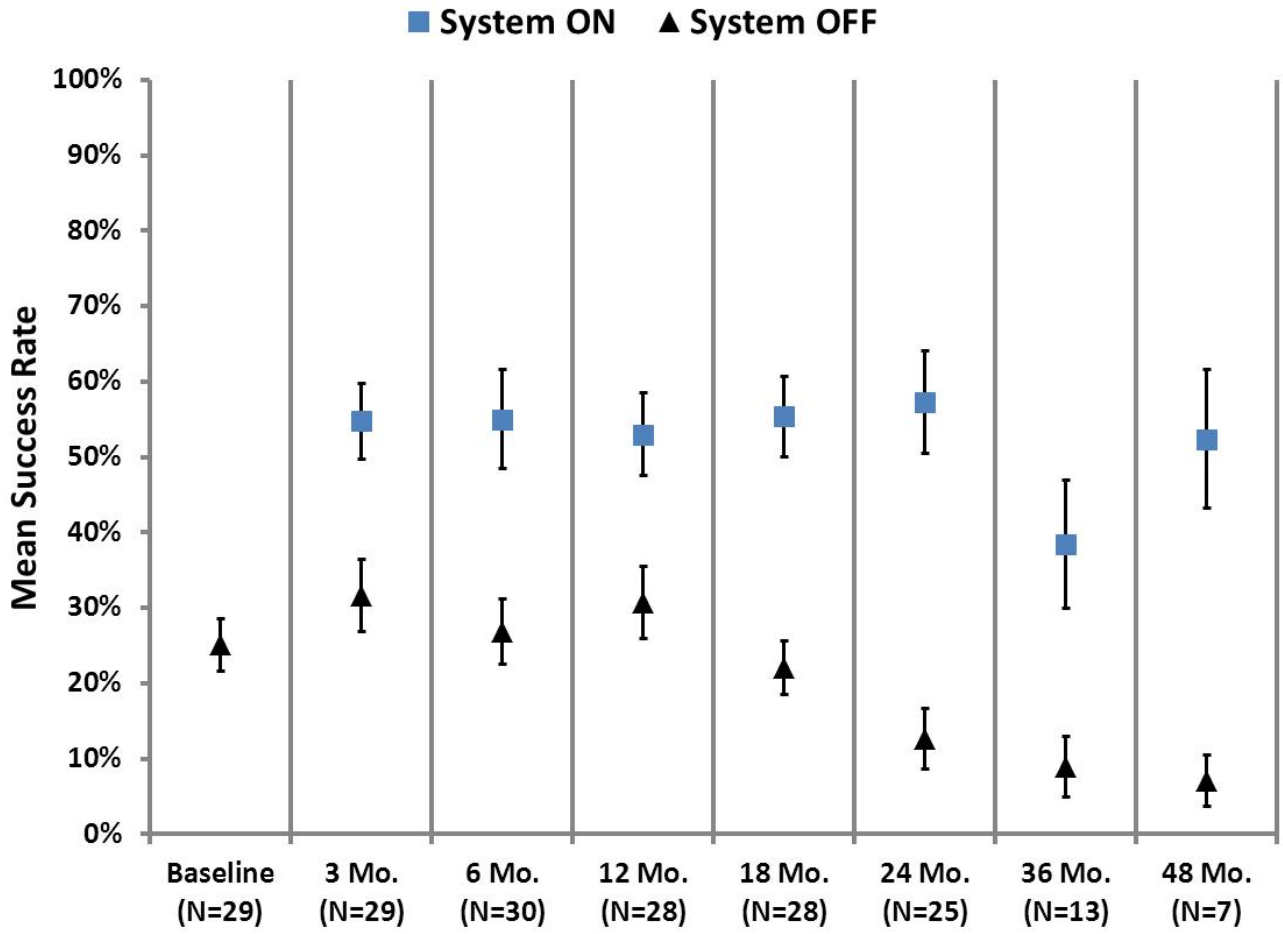


- **Subset of subjects (N=4) could read words using Argus II System**

Secondary Study Endpoints

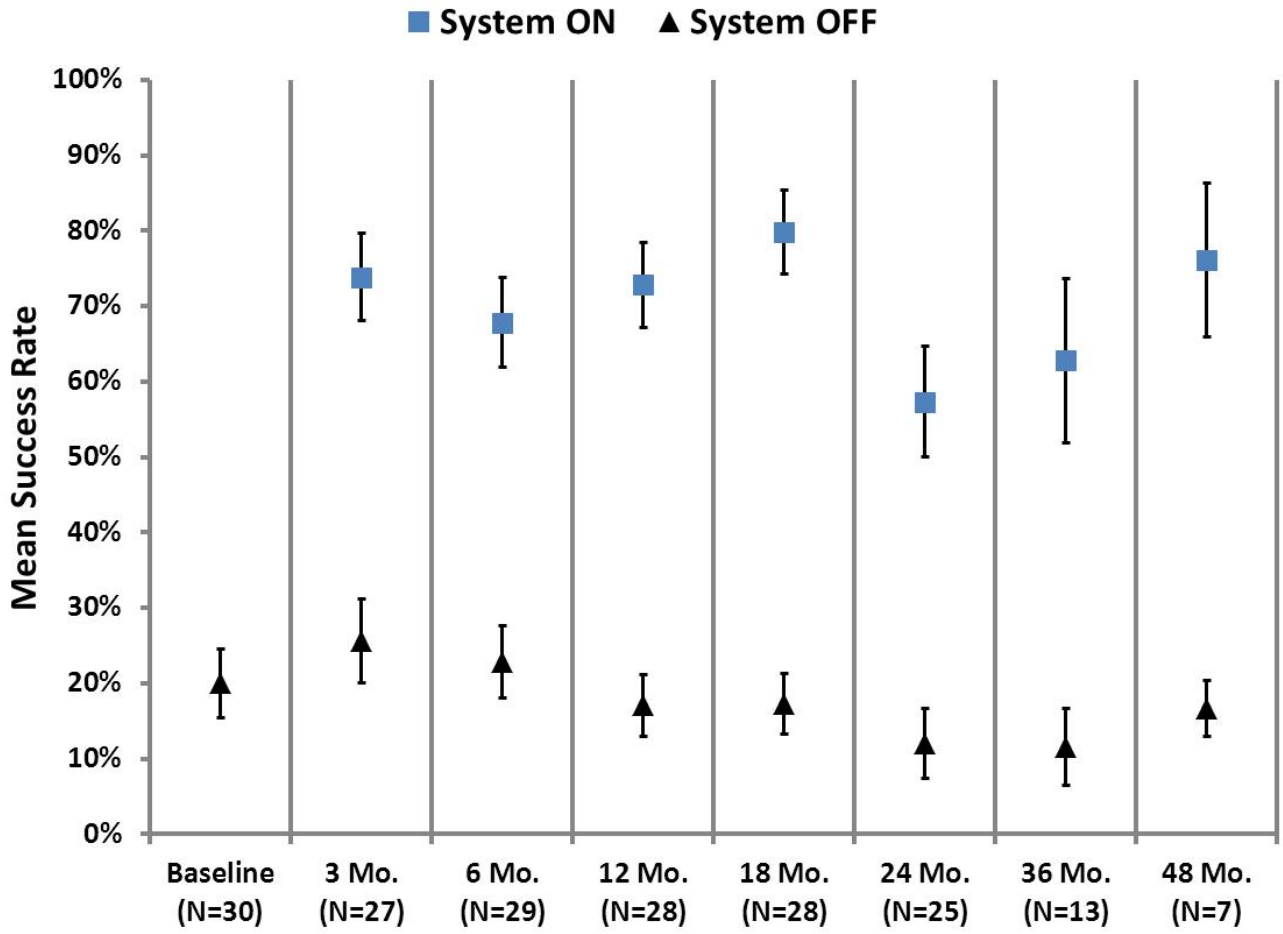
- Probable Benefit – Functional Vision and Quality of Life (QOL)
  - Orientation and Mobility Tests
  - Functional Low-Vision Observer Rated Assessment (FLORA)
  - Functional Vision Tasks (additional research)
    - Sock Sorting
    - Sidewalk Tracking
    - Direction of Walking

Orientation and Mobility - Door Task



- **Subjects were better at finding a door with the Argus II System ON**

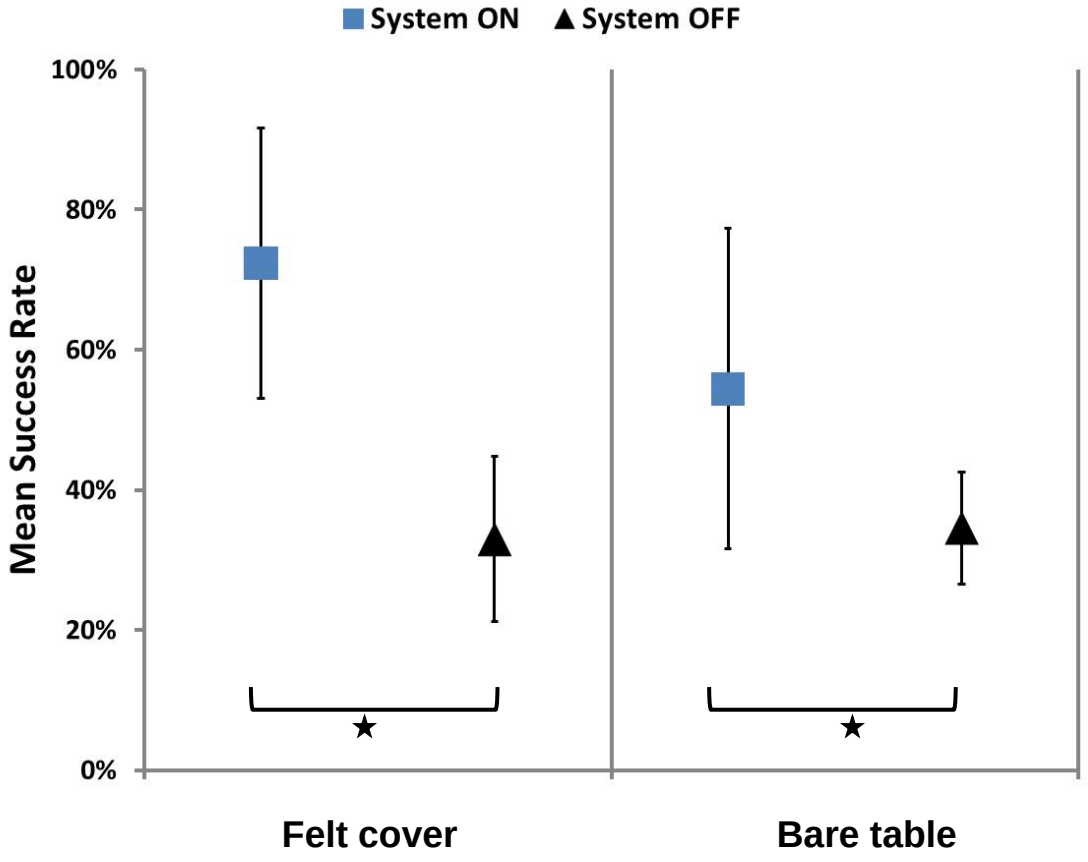
Orientation and Mobility – Line Task



- **Subjects were better at following a line with the Argus II System ON**

Sock Sorting

n = 28 subjects



★ p<0.01, t-test assuming unequal variance

- **Subjects performed significantly better on the sock sorting task with the System ON vs. OFF**

Sidewalk Tracking

n = 27 subjects

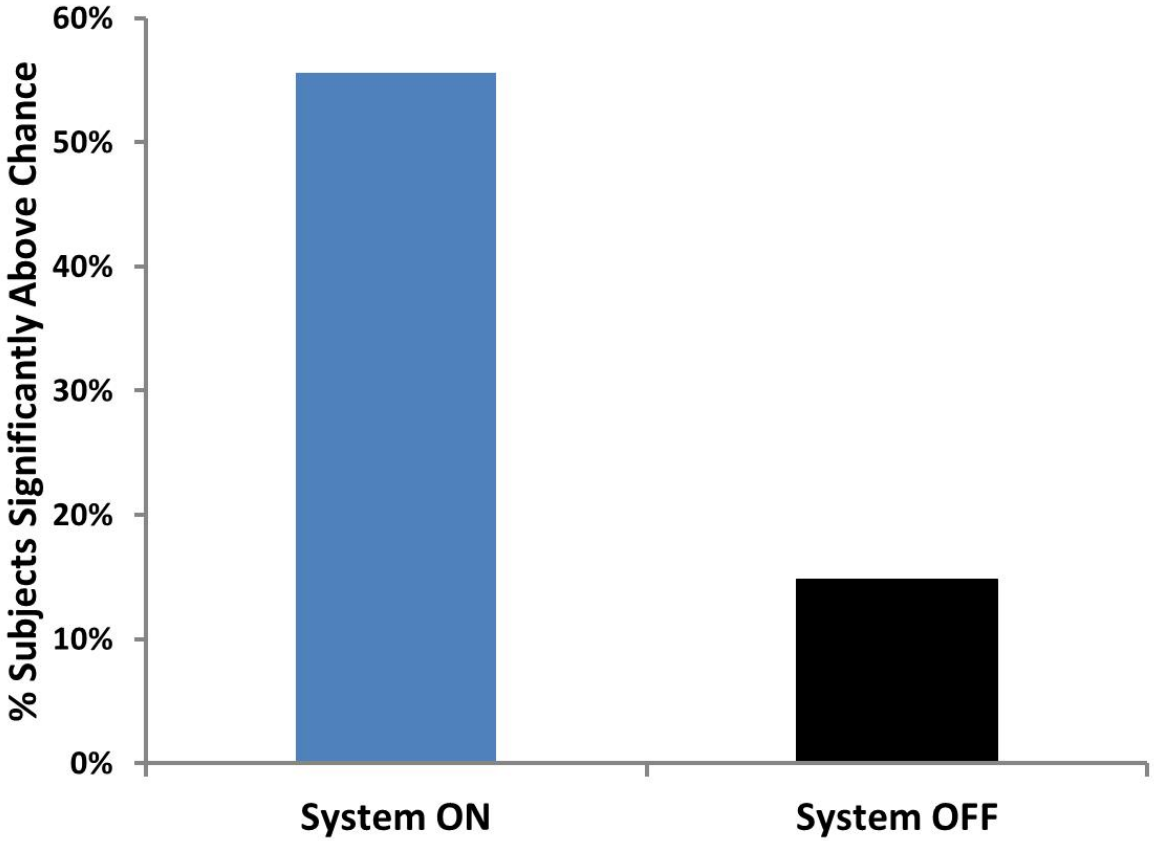
Mean # of out of bounds	
System ON	**System OFF**
4.9 ± 2.6	6.9 ± 3.0

★ p<0.05, Paired t-test

- **Subjects performed significantly better (i.e. fewer out of bounds) with the System ON vs. OFF.**

Direction of Walking

n = 27 subjects



- **56% of subjects performed better than chance* with the System ON (vs. 15% with System OFF)**

***p<0.05, two-tailed binomial distribution**

Functional Low-Vision Observer Rated Assessment (FLORA)

FLORA assessments were performed by trained, certified, low-vision therapists

1) In-depth interview using a questionnaire (14 questions)
   - Purpose: Understand effect of Argus II System on subject's lives
2) Observe subject's ability to perform tasks in and around their homes
   - Purpose: Rate how subjects performed everyday tasks with the Argus II System ON vs. OFF
3) Therapist wrote a case-study narrative for each subject they assessed
   - Answer the question: Does the Argus II System provide benefit, detriment, or no impact to the subject, and if so, in what specific ways?

FLORA – Therapist-rated tasks (Part 2)

Analysis of the FLORA

- To summarize the results from the FLORA, an independent therapist (Duane Geruschat) reviewed all the case study narratives
- He categorized the effect of the Argus II System on each subject's life as either:
  - Positive
  - Mild positive
  - Prior positive
  - Neutral
  - Negative

FLORA – Part 3 Results

n = 26 subjects

Effect of Argus II System on subjects' functional vision/quality of life:

Positive	Mild positive	Prior positive	Neutral	Negative
35% (9)	27% (7)	15% (4)	23% (6)	0%

Overall:

Positive	No positive effect
77% (20)	23% (6)

% subjects (n)

- **Argus II System improved functional vision and/or well-being in the majority of subjects.**

Probable Benefit Conclusions

- Probable Benefit evaluated using 9 different assessments that targeted 3 key domains:
  - Visual Function
  - Functional Vision
  - Quality of Life

- **Totality of the data demonstrate the probable benefit the Argus II System provided to subjects**
- **Benefit sustained beyond 2 years**

Study Conclusions

- **Long-term follow-up data collected on a reasonable sample size given a rare population.**
- **Study demonstrated a reasonable assurance of safety**
- **Totality of data collected from multiple assessments demonstrated the probable benefit of the Argus II System**

Study demonstrated the probable benefit to health of the Argus II System outweighs the risk of injury or illness to these profoundly blind patients

Second Sight

Training
and
Post-Approval Study*

Gislin Dagnelie, PhD

Associate Professor of Ophthalmology,
Johns Hopkins University

* FDA has not formally reviewed the training and post-approval study.

New Site Training & Support Program

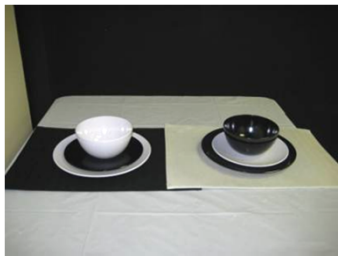
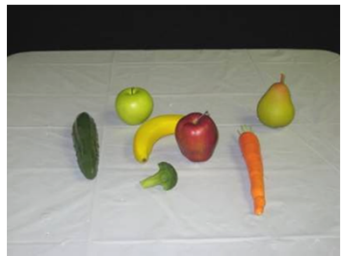
- Second Sight representatives will provide training to surgeons, device fitting specialists, and vision rehabilitation specialists:
  - Instructions for use and user manuals
  - Hands-on device use
- Second Sight surgical support team will be present at initial cases
- Experienced surgeon will be present at 1st implant at a new hospital
- Second Sight technical support team will be present at initial fitting sessions
- Experienced therapist will be present at 1st vision rehabilitation session

Second Sight is committed to supporting new centers and patients to ensure successful outcomes.

Vision Rehabilitation Program

- Vision rehabilitation is designed will help patients incorporate the Argus II System into their everyday lives
- Patients will receive vision rehabilitation from a trained low-vision therapist
- In-home vision rehabilitation sessions
  - Based on well-established low-vision and blind rehabilitation approaches customized for Argus II
  - Begins four weeks post-implant
  - Individualized program based on the goals of the patient
    - Learn to incorporate the Argus II System into his or her life
  - Instructional Kit for additional practice



Proposed Post-Approval Study for Existing Study Subjects

- Continue to obtain long-term follow-up on the subjects enrolled in the IDE clinical trial
- Study has already been extended to follow up subjects through 7 years post-implant in the U.S.
- In Europe, study has been extended through 5 years post-implant

Second Sight

Proposed Post-Approval Study for New Patients

- Main objective: Continue to monitor the safety of the Argus II System
- Post-market study currently underway in Europe
- Propose to use the same study design in the US
- Non-randomized, controlled, prospective, multi-center study
- Enroll until 45 subjects are participating or 30 subjects have reached 1-year follow-up, whichever comes first
- Primary endpoint
  - Safety
- Secondary endpoints
  - Visual function
  - Activities of daily living

Post-Market Conclusions

- Second Sight has a well-established training program for new sites
- Second Sight is prepared to continue to closely monitor the results from the device in the post-market setting
- HDE condition of approval requires additional IRB oversight at all implanting centers

Risk-Benefit Analysis and Conclusions

Suber Huang, MD

Independent Medical Safety Monitor, Argus II Study

President, American Society of Retina Specialists

Vice-Chair, Department of Ophthalmology & Visual Sciences
Case Western Reserve University School of Medicine

Treatments for RP – An Unmet Clinical Need

- Only about 250 Americans become profoundly blind and eligible for the Argus II system each year
- Devastating impact on lives of patients and families
- Focus has been on preservation, enhancement, and restoration of sight in mild and moderately vision-impaired individuals
- Tools to assess vision in patients with profound visual loss or no sight are limited because of the lack of treatment options

➢ **There is a need for a treatment in patients with RP and blindness**

Baseline Risk of Argus II Implant is Low

- Patients have profound visual loss with minimal to no remaining ability to perceive light
- Pre-operatively, they have no functional vision for activities of daily life
- Argus II does not prevent someone from receiving future treatments
  - Device is implanted in the worse eye
  - Argus II system has been safely explanted
  - In the worst case, the fellow eye is unaffected

Risk Profile is Acceptable for this Patient Population

- Adverse events were expected, manageable, and successfully treated using standard techniques
- Only one device explanted to resolve an AE
- Refinements made to surgical procedure and implant led to modest reduction in AEs

- **No systemic injuries or permanent visual impairments were associated with implantation or use of Argus II System**

Clear Evidence of Probable Benefit

- Argus II subjects demonstrated the ability to:
  - Localize light, recognize large characters, identify direction of a moving line, obtain a measurable visual acuity (up to 1.8 logMAR), read words
  - Follow a line, find a door, sort socks, track a sidewalk, and determine the direction of a moving person
  - Perform real-world tasks such as locating people, orienting in unfamiliar environments, avoiding obstacles
- Argus II System provided psychological benefits that are extremely important, such as feeling more socially connected, enjoying seeing again

➢ **These benefits are highly valued by the blind and profoundly influence the lives of patients**

RP - A Patient's Perspective

- A relentless disease, often diagnosed in young adults
- Visual field constriction (loss) progresses at 5-10% per year and can lead to complete blindness
- With no other treatments available, patients and their families face a future with little or no hope
- Blind patients are willing to accept potential risk for the possibility of partial vision restoration

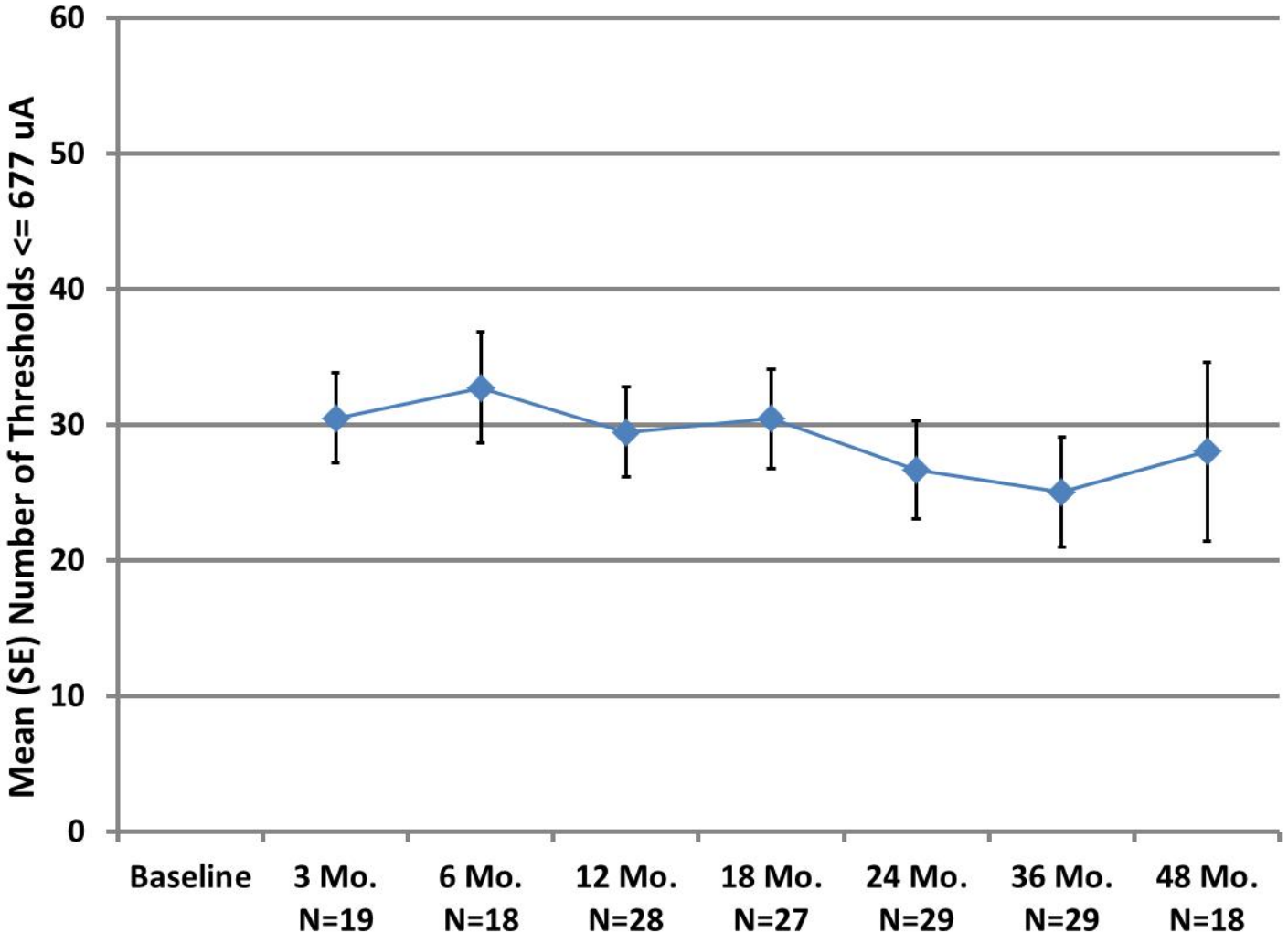
➢ **For the first time, this device offers patients and their doctors an option to improve vision and quality of life**

Conclusions

- The Argus II system improves the lives of patients with RP
- Benefits in improved vision, function and quality of life outweigh the risks of this treatment
- The regulatory criteria for HDE approval have been met
- Patients, their families, and doctors want and need options to help patients with this incurable disease
- **Approval of this device will alleviate suffering and provide hope to many Americans**

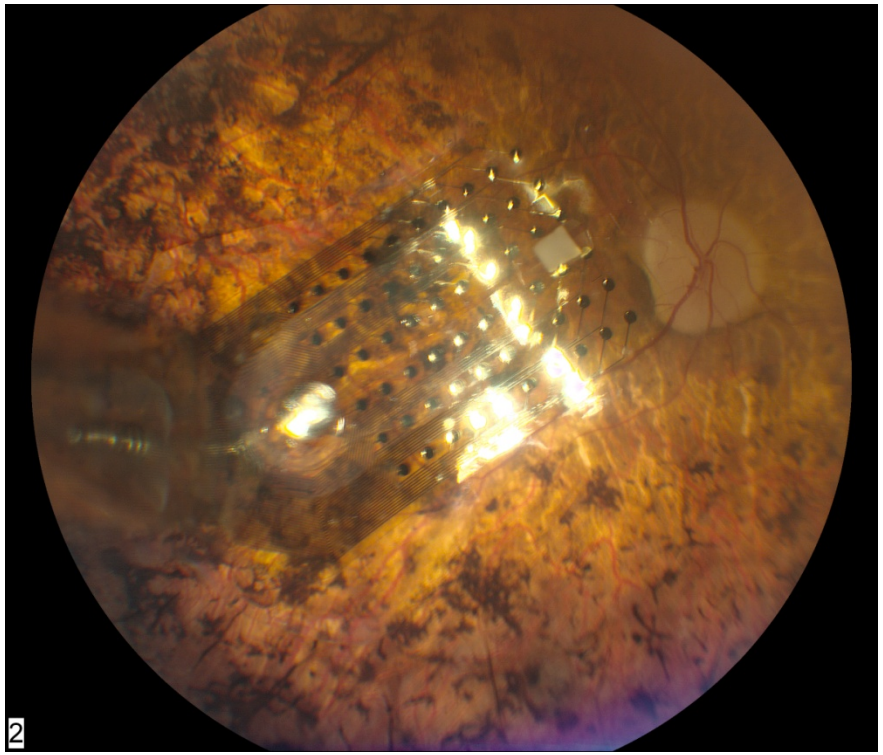
Thank you

Average Number of Thresholds over Time



Explanted Subject

12 Months Post-Implant



12 Months Post-Explant